REVISED **SYNOPSIS**

"SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF NITROGEN CONTAINING HETEROCYCLES USING RECYCLABLE CATALYST"

" पुनः चक्रित करने योग्य उत्प्रेरक के उपयोग द्वारा नाईट्रोजन युक्त विषमचक्रीय यौगिकों का संश्लेषण, अभिलक्षण एवं जैविक सक्रियता"

A
SYPNOSIS
SUBMITTED TO THE
M.D.S. UNIVERSITY, AJMER
FOR DOCTOR OF PHILOSOPHY
(FACULTY OF SCIENCE)

By:

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APPENDIX -

MAHARSHI DAYANAND SARASWATI UNIVERSITY,
AJMER

Format for Outline of Proposed Research work
(to be supplied in Six copies)

1.Name of Scholar (In English) : **NARENDRA NIRWAN**

(In Hindi) : नरेन्द्र निर्वाण

2.Title of the Research Work:

(In English) : **"SYNTHESIS,CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF NITROGEN CONTAINIG HETEROCYCLES USING RECYCLABLE CATALYST"**

(In Hindi) : *" पुनः चक्रित करने योग्य उत्प्रेरक के उपयोग द्वारा नाईट्रोजन युक्त विषमचक्रीय यौगिको का संश्लेषण, अभिलक्षण एवं जैविक सक्रियता"*

3 Location

a. Institution/Department where the work is to be done: **S.D.GOVT.COLLEGE ,BEAWAR**
b. Geographical area of Investigation, if any : **NIL**

4. Introduction Importance of Proposed Investigation, Objectives: ENCLOSURE-1
5. Review (Work already done on the subject of proposed Research Study.) : ENCLOSURE-2
6. Research Gaps identified in the proposed field of investigation.(Based on the review): ENCLOSURE-3
7. Major Hypothesis, if any: ENCLOSURE-4
8. Research Methodology: ENCLOSURE-5
9. List of References cited: ENCLOSURE-6

(Narendra Nirwan)
Candidate

Outline Approved.

(Dr. Chandresh Pareek)
Supervisor

APPENDIX - VI

MAHARSHI DAYANAND SARASWATI UNIVERSITY, AJMER

Certificate By Supervisor
Certified that:

1. I am willing to guide the research work of **Mr. NARENDRA NIRWAN** on the above subject if he/she is registered for Ph.D.
2. To the best of my knowledge, the subject selected has not been studied and is not being studied so far in any University.
3. The subject is of sufficient scope to keep the candidate engaged for two years.
4. The subject will lead to a valuable contribution. I have seen and approved the outline of proposed research work submitted by the candidate.
5. I have **01** (give numbers) Research candidates registered under my supervision and the serial number of this candidate whose application is being forwarded for registration is **01** (give the serial number)
6. The candidate is not in a close relation.

(Dr. Chandresh Pareek)
Supervisor

Certified that the available facilities will be extended to Mr. **NARENDRA NIRWAN** for research work if he is registered for Ph.D..

Principal
S.D. Govt. College, Beawar
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Head
Department of Chemistry
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ENCLOSURE – 1

INTRODUCTION, IMPORTANCE OF PROPOSED INVESTIGATION AND OBJECTIVES

Heterocycles form one of the most important classes of organic molecules both in view of their economic importance and their mere production quantity. *N*-heterocycles display a large spectrum of interesting properties in many fields such as medicinal chemistry, chemical biology and material science. Bacteria of genus *Xenorhabds* is reported to contain rich source of metabolites exhibiting antibacterial, antifungal activities etc. The compound reported from this genus includes indole derivatives[1]. Discovery of new active compounds often starts with the identification of a particular class of heterocycles which show a desired biological activity and create several libraries for the preparation of several potential active drugs.

Indole is aromatic heterocyclic organic compound. It is a bicyclic structure, consisting of a six membered benzene ring fused with a five membered nitrogen containing pyrrole ring. The participation of the nitrogen lone electron pair in the aromatic ring means that indole is not a base, and it does not behave like a simple amine. Bacteria can produce indole as a degradation product of the amino acid tryptophan. It occurs in human feces and has an intense fecal odor. At a very low concentration, however, it has a flowery smell[2], and is a constituent of many flower scents (such as orange blossoms) and perfumes. The name indole is a portmanteau of the words indigo and oleum, since indole is first isolated by treatment of the indigo dye with oleum. The chemistry of indole have been investigated because of wide spread occurrence and basic structural unit of various type of natural products with useful physiological properties[3-6]. Compounds with an imidazole ring system have many pharmacological properties and play important roles in biochemical processes[7]. Many of the substituted imidazoles are known as inhibitors of fungicides and herbicides, plant growth regulators and therapeutic agents[8]. Recent advances in green chemistry and organometallic chemistry have extended the boundary of imidazoles to the synthesis and application of a large class of imidazoles as ionic liquids and imidazole related N-heterocyclic carbenes[9].

Ionic liquid (IL) technology when used in place of classical organic solvents, offers a new and environmentally benign approach toward modern synthetic chemistry.[10] Ionic liquids have some advantages included low vapor pressure, thermal stability, reusability,

talent to dissolve many organic and inorganic substrates.[11] Recently ionic liquids have been successfully employed as dual reagent (solvents + catalytic) for a variety of reactions but their use as catalyst under solvent-free conditions need to be pay more attention.[12]Ionic liquids with acidic counter ions involving 1-hexyl-3-methyl-imidazolium bisulfate ([hmim][HSO_4]),[13] 1-butyl-3-methylimidazolium dihydrogen phosphate ([bmim][H_2PO_4]),[13] 1-[2-(2-hydroxy-ethoxy)ethyl]-3-methyl-imidazolium bisulfate ([heemim][HSO_4]),[13] 1-butyl-3-methyl-imidazolium chloroaluminate ([bmim]2$AlCl_3$)[14] and 1-butyl-3-methyl-imidazolium bisulphate ([bmim][HSO_4])[15] can be used as good acid catalysts. There have been a number of excellent ionic liquid reviews concerning their chemical and physical properties [16-20] and applications in synthesis and catalysis.[21-27]

The application of heterogeneous acid catalysts in place of homogeneous acid catalysts in organic synthesis is an attractive area of research in the laboratory as well as in the industrial context. The advantages of the heterogeneous catalysts over the homogeneous catalysts include stability (toward air and moisture), lack of corrosion, ease of handling, recovery and regeneration[28]. It has been reported that Keggin-type heteropolyacid $H_4[PMo_{11}VO_{40}]$ is a highly efficient solid acid catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles. The four-component condensation of benzil, benzaldehyde derivatives, primary amines and ammonium acetate catalyzed by Keggin heteropolyacids such as $H_3[PW_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, $H_3[PMo_{12}O_{40}]$, $H_4[PMo_{11}VO_{40}]$, $HNa_2[PMo_{12}O_{40}]$ as an efficient and facile one-pot synthesis of tetrasubstituted imidazoles has been successfully performed[29].The catalyst could be reused after a simple work-up, with a gradual decline of its activity being observed. The reaction appeared to be heterogeneously catalyzed. High yields, relatively short reaction times, simplicity of operation and easy work-up were some advantages of this protocol[30]. We have discovered an efficient and environment friendly procedure for the synthesis of 3-substituted indole with imidazole. Catalysts can be recovered and reused for the synthesis. After purification of all the synthesized compounds, structure will be characterized by spectral studies like I.R., N.M.R., etc. Toxicity of synthesized products will be measured by fungicidal studies. Density can be used to determine the concentration of solutions in certain instances. The determination of density of certain physiological liquids is often an important screening tool in medical diagnosis. The viscosity of fluid is its resistance to flow. It is a quantitative property of fluid and can be used in quality control applications of oil, paints, drugs or the fluids where flow is a critical property[31].

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ENCLOSURE – 2

REVIEW OF WORK ALREADY DONE ON THE SUBJECT OF PROPOSED RESEARCH STUDY

From 1866 up through the first decade of the twentieth century, indole chemistry occupied a prominent place in numerous laboratories. As other dyestuffs took the spotlight from indigo and related structures, the interest in indole chemistry diminished in intensity. The demonstration in the 1930s, that a large number of alkaloids contain the indole nucleus[32] the recognition of the importance of tryptophan in human and animal nutrition[33] and the discovery of the plant hormones[34-36]served to bring about a renaissance in indole chemistry that has been most fruitful. Indole, *dl* tryptophan and several other indole derivatives readily available today in quantity, but the studies of practical methods for their preparation have greatly enriched organic chemistry.

In the vast heterocyclic structural space, the indole nucleus occupies a position of major importance, including fused derivatives, from the basis of the range of pharmaceuticals and a high level of activity continues in the search for new indole-based medicinal agents[37]. It is well known that indole behaves as an enamine towards electrophiles and undergoes Michael addition to electron-deficient alkenes. In contrast, its dienophilic has been reported only on a few occasions. The Diels-Alder adducts of indole could potentially be useful starting materials in the total synthesis of indole monoterpenoid alkaloids and ellipticine-type compounds with antitumor activity[38].

The meridianins are a family of indole alkaloids which were isolated from subantartic tunicate *Aplidium meridianum*[39]. The basic structure of these compounds consists of an indole nucleus substituted at C-3 by a 2-aminopyrimidine ring. Other examples of heterocycles substituted by an aminopyrimidine ring have been reported among marine natural products. The natural meridianins have previously been synthesized by a cross coupling reaction between the indole and pyrimidine moieties[40]. Biologically active molecules isolated from marine organisms constitute an ever-growing subset of all natural products collected, and among them are some of the most potent antitumor and cytotoxic agents. The dragmacidins represents the emerging class of bioactive marine natural products obtained by an exhaustic set of protocols from a number of deep-water spongs[41]. A variety of biologically active metabolites containing the indole ring have been identified from marine organisms. Among these, 3-substituted indoles represent an emerging structural class of

marine alkaloids based upon their high degree of biological activity. The 3- substituted indole alkaloids with additional heterocyclic rings like imidazole (nortopsentins, topsentins)[42-43]; substituded imidazole (discodermindole)[44] (trachyclaindole)[45]; maleimide, oxazole, pyrimidine have been isolated and shows cytotoxicity towards murine tumor cells. However 5 - substituted indole derivatives with imidazole ring have not been studied thoroughly. Therefore we have chosen the synthesis of 5-substituted indole derivatives with imidazole ring substituted at 3 - position.

ENCLOSURE – 3

RESEARCH GAPS IDENTIFIED IN THE PROPOSED FIELD OF INVESTIGATION

References on the related subject reveal the importance of the proposed field. For this purpose literature survey from different universities and searching through internet includes the following plan. Synthetic, antifungal, antimicrobial studies on 5-substituted and some new indoles with 3-substituted nucleus are still open to study.

Synthesis and spectral studies of various heterocycles with 'Nitrogen' as heteroatom have been done. A slight difference in substitution pattern provides a series of new synthesized compounds. The physico-chemical and analytical data on viscosity, surface tension, molar volume of synthesized compounds are not available. Therefore to investigate the nature and their solution behavior in various solvents, the present work is necessary to be done and this stimulates our interest to study these parameters for research.

ENCLOSURE – 4

MAJOR HYPOTHESIS, IF ANY

The substituent at 3-position of the indole ring is often an additional heterocyclic ring: imidazole (nortopsentins and topsentins); dihydroimidazole (discodermindole, trachyclodindole, rhopaladins); maleimide (didemidines); oxazole (martefragin, imazol); oxadiazine; and piperazine (dragmacidins).[46] These alkaloids, which show cytotoxicity towards murine tumor cell lines, have a brominated and/or hydroxylated indole nucleus with a pyrimidine ring as substituent at 3-position[47]some indole substituted pyrimidines was reported as anti-cancer agents.[48] Indole-3-carbinol is a compound used as treatment agent for breast and other types of cancers, and may have beneficial effect in the management of *Herpes simplex* virus (HSV) and human papilloma virus (HPV).[49] The above applications stimulated our interest to extend synthetic investigations. Biocidal studies of these compounds will also provide an important account of information about their industrial utilization. In the present work the physical, analytical and spectral studies will be investigated. The study about their solution behavior will provide fundamental information about the molecule along with various interactions between solute and solvent molecules. The proposed research work will generate new aspects in biological and pharmacological fields due to the biological importance of synthesized compounds.

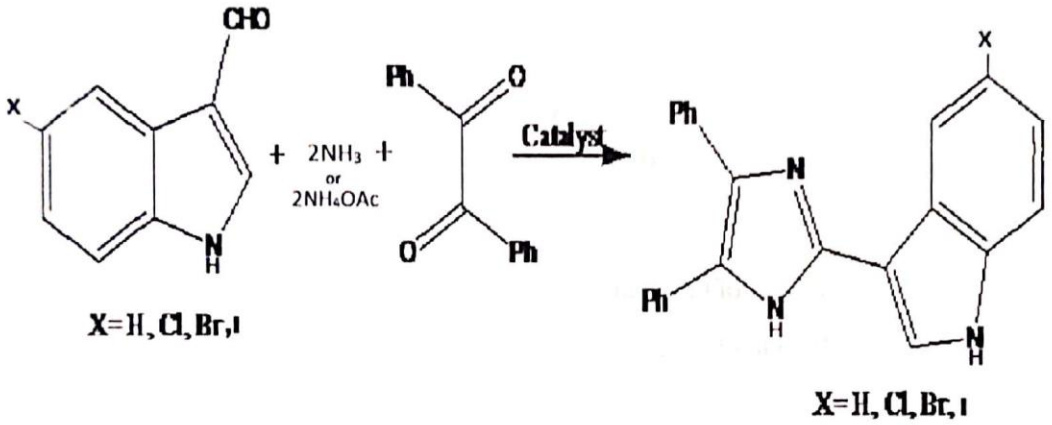
Indole and its derivatives are reported to have wide spectrum antiparasitic activity. Apicidin, the indole alkaloid is reported to have potent antimalarial activity. Studies on apicidin suggested that indole nucleus is key constituent of enzyme binding activity.

ENCLOSURE – 5

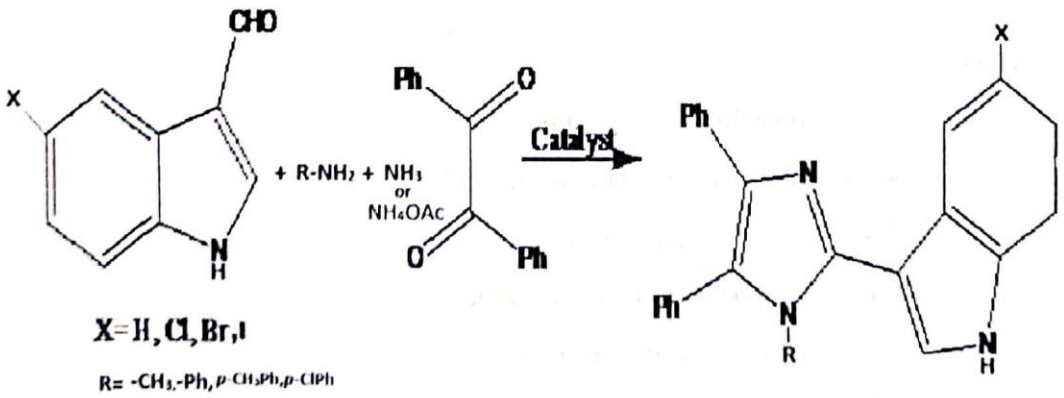
RESEARCH METHODOLOGY

1. SYNTHESIS:
   a) The synthesis of N- containing hetrocycles using Recyclable Catalysts such as heteropoly acid/ionic liquid will be done under laboratory condition.
   b) Recyclability of catalysts for products.

SCHEME - (I): Synthesis of desire products by reaction between 5-substituted indole, benzil and ammonia or ammonium acetate in presence of catalyst.



SCHEME - (II): Synthesis of desire products by reaction between 5-substituted indole, benzil, amine and ammonia or ammonium acetate in presence of catalyst.



STRUCTURAL PARAMETERS:

Purity of compounds will be confirmed by thin layer chromatography and will be characterized by their spectral studies.

BIOCIDAL STUDIES :

Screening the biological activities and applications of these compounds as antifungal agents, it is proposed to study their toxicity against various fungi.

PHYSICO-CHEMICAL PROPERTIES

Density and viscosity will be calculated in different non aqueous media like Benzene and Alcohol in different compositions. To measure the densities of solution and the results will be calculated using following equation.

$$d = \frac{W}{W_o}$$

Where,

W = Weight of the solution.

W_o = Weight of water.

The following relation is used to calculate the molar volume.

$$V = \frac{X_1M_1 + X_2M_2 + X_3M_3}{d}$$

Where,

X_1 = Mole fraction of solution.

M_1 = Molecular weight of compound.

X_2 = Mole fraction of benzene.

M_2 = Molecular weight of benzene.

X_η = Mole fraction of methanol.

M_3 = Molecular weight of methanol.

d = Density of solution.

The viscosity of solution will be calculated by using following relations.

$$\frac{\eta_o}{\eta} = \frac{d_o t_o}{dt}$$

Where,

η_o = Viscosity of known solution.

η = Viscosity of unknown solution

d_o = Density of known solution.

d = Density of unknown solution.

t_o = Time of flow of known solution.

t = Time of flow of unknown solution.

ENCLOSURE – 6

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